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TITLE: Intervention Study of Flaxseed in Postmenopausal Women: Effects on Hormonal Biomarkers of Breast Cancer Risk

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13. ABSTRACT (Maximum 200 Words)

The objective of this study is to determine if flaxseed supplementation to usual diet in postmenopausal women has a beneficial effect on important hormonal biomarkers of breast cancer risk. To date, a total of 47 eligible study participants have been successfully enrolled in the study from University of Massachusetts area; we anticipate that we will achieve the required sample size of 50 study subjects by 31 August 2003. Participants receive 6 weeks of usual diet plus 12 grams of raw flaxseed, followed by six weeks of usual diet plus 24 grams of raw flaxseed. Serum and urine are collected at baseline, 7 weeks and 13 weeks. At the completion of the study, serum and urinary levels of hormonal biomarkers of breast cancer risk will be measured (i.e., serum hormone levels: estradiol, testosterone, sex hormone binding globulin; urinary estrogen levels: 2/4-OHE1 and 2/16alpha-OHE1, genotoxic estrogen metabolites:total estrogens).

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Introduction: It has been hypothesized that plant-derived estrogens (phytoestrogens) play an important role in the etiology of breast cancer. One class of phytoestrogens known as lignans are present in a variety of fruits, vegetables, and grains, but flaxseed is by far, the richest source. Laboratory and cross-sectional studies indicate that lignans are favorably associated with important hormonal biomarkers of breast cancer risk, including elevated serum levels of sex-hormone binding globulin and lower serum levels of estradiol and testosterone. The objective of this study is to determine if flaxseed supplementation to usual diet in postmenopausal women has a beneficial effect on important hormonal biomarkers of breast cancer risk. The specific aims of this study are to determine if (1) flaxseed intake lowers serum levels of estradiol and testosterone and increases serum levels of sex-hormone binding globulin; (2) flaxseed intake increases the urinary excretion ratio of 2/4-OHE1 and 2/16a-OHE1 and decreases the urinary excretion ratio of genotoxic estrogen metabolites to total estrogens (16a-OHE1 + 4-OHE2 + 4OHE1)/total estrogens; and (3) higher doses and longer duration of flaxseed intake results in greater changes to the aforementioned variables. Participants in this study will be volunteers recruited from the University of Massachusetts area. The pre-post intervention study will involve a total of 50 postmenopausal women. Participants will receive 6 weeks of usual diet plus 12 grams per day of raw flaxseed, followed by 6 weeks of usual diet plus 24 grams per day of raw flaxseed. Serum and urinary levels of hormonal biomarkers of breast cancer risk will be assessed at baseline, 7 weeks, and 13 weeks. The project will establish whether flaxseed may be a useful dietary strategy in the prevention of breast cancer. *After discussion with the Core, no further justification regarding the dosing schedule is necessary because this information is detailed in the protocol.*

Body: Study participant recruitment and data collection is currently underway. Laboratory assays and statistical analyses will be conducted after all data collection is complete. A total of 47 eligible study subjects have been enrolled in the study; the project total of 50 study subjects is anticipated by 31 August 2003. We have completed 47 introductory visits, 39 baseline visits, 27 1st follow-up visits, and 19 2nd follow-up visits. Thus, data collection has been completed on 19 study subjects, and data collection is underway on an additional 28 women.

Recruitment was slow in the first several months, in part because study particpants were reluctant to participate over the holiday season, and few women were willing to abstain from alcohol. Recruitment has substantially increased over the last four months, largely due to our intensified effort in recruiting study subjects through locally-distributed free newspapers and because of a DOD-approved protocol change to allow women to consume moderate amounts of alcohol.

Initially, women are not allowed to drink alcohol while participating in the study. To allow us to recruit study subjects in a timely fashion, we obtained permission to modify the eligibility criteria to allow women who drink moderately to participate in the study; that is, women who typically drink 7 drinks or less per week and no more than 2 drinks per day are eligible to participate. Study subjects are required to maintain their usual alcohol intake patterns throughout the study.

This modification is justified scientifically based on a recent clinical study demonstrating no change in serum levels of estradiol or testosterone (these are the two outcomes examined in this study) associated with moderate alcohol intake [Dorgan JF et al., Serum hormones and the alcohol-breast cancer association, J Natl Cancer Inst 2001:93:710-5]. Moreover, there is no a priori reason to believe that the study population will systematically increase or decrease their alcohol intake between the baseline and intervention study periods. Thus, any background level of alcohol on the study outcomes will be the same at the baseline and intervention blood draws. Finally, as we already collect information on recent alcohol intake in 7 day diet record administered three times during the study, we would be able to take any recent changes in level of alcohol into account in the analysis. *This change was approved by the Department of Defense, and the Core was notified of this approval in an email sent from Ms. Caryn Duschesneau on January 27, 2003*

Key Research Accomplishments,

After discussion with the Core, the following items remain as key research accomplishments.

- The protocol was submitted and approved
- Data collection is complete on 19 study participants
- Data collection is underway on an additional 28 study participants
- A total of 47 eligible stubjects have been enrolled; the project total of 50 study subjects is anticipated by 31 August 2003.

Other results from this study are not yet available for this study. Blood and urine specimens will be analyzed after all study subjects have completed data collection. As stated in the protocol, specimens will be analyzed all at one time so that the assay, reagants and technician will be the same for all specimen, thereby maximizing reliability of the assay.

Contractual Issues

The grant proposal requested only travel funds ($1500) during the third year to attend the Department of Defense breast cancer meeting. No salaries or other support were requested in the third year. *After discussion with the Core, no additional justification of the 36-month performance period is necessary.*

Reportable Outcomes:

A funding application was submitted to the Americian Institute of Cancer Rseearch to examine the effects of dietary flaxseed on other blood biomarkers of cancer risk (i.e., insulin-like growth factor, insulin-like growth factor binding protein, c-peptide) using

remaining blood specimens from this study. The title of this proposal is "Intervention Study of Flaxseed in Postmenopausl Women: Effects on Biomarkers of Cancer Risk". *After discussion with the Core, the grant number is not necessary as this is not a DOD grant.*

References: Not Applicable

Appendices: Not Applicable.